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## Functional magnetic resonance imaging of tinnitus

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*Document Version*

Publisher's PDF, also known as Version of record

*Publication date:*

2010

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Lanting, C. P. (2010). *Functional magnetic resonance imaging of tinnitus*. s.n.

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Summary

# Summary

Tinnitus resides between the ears

## Tinnitus, a pathology between the ears

Besides tissues like bone, fluid and brain tissue, there is more between the ears, at least that is what the google-results show us after a search. Obesity, feeling cold and even an orgasm can all be found between the ears. This is not really strange if you think about it. The brain processes sensory signals in such a way that we are able to perceive the world around us. They also co-ordinate the muscles which make us either move or stop us from moving. If everything goes according to plan these processes may not be noticeable. Yet, if there is interruption of some kind we will notice it, either directly or somewhat later.

Problems in communication may be caused by hearing loss—a problem with the auditory senses that has its roots outside the central nervous system (and therefore peripheral). Parkinson's disease, on the contrary, is an example of a degenerative affection of the central nervous system and is characterized by motor dysfunction (among others) .

There is also a category of affections where a change in the peripheral function may lead to a change at a central level. One example is phantom-limb pain which may start after amputation of a limb. The sensory input to the central nervous system is decreased which may cause the complaints of pain in the phantom limb. This thesis describes a number of studies to a possible analogous problem in the auditory system: tinnitus.

## Tinnitus

Tinnitus may be the term for a number of possible different pathologies that all lead to the same percept: a sound that is only heard by the patients. A common theory describes the etiology of tinnitus as the disruption in the balance between excitatory and inhibitory input to the auditory cortex. If, for example, the auditory input is diminished through a peripheral hearing loss, it may cause the activity in the central auditory system to increase. Since the loudness of sound is also coded by the level of activity, an increase in the (spontaneous) activity may effectively lead to the percept of a sound: tinnitus.

## Imaging techniques and tinnitus

In an attempt to objectify this abnormal levels of activity *functional magnetic resonance imaging* (fMRI) was used. This technique measures the change in the vascular oxygen level in the brain, which is caused by (task-related) changes in the levels of neural activity. Chapter 2

In a number of studies on tinnitus, both fMRI as *positron emission tomography* (PET) have been used to show differences between subjects with tinnitus and subjects without. A number of experimental paradigms have been used. A common method measures sound-evoked responses in patients and compares it to those in subjects without tinnitus. From work performed in animals with tinnitus they found—in addition to the increased levels of spontaneous activity—an increased sound-evoked response. This might also hold for patients with tinnitus.

Another methods studies a specific group of subjects that have the ability to modulate the loudness of their tinnitus by eye-movements or jaw-movements. By measuring the activity during this modulation and during 'rest' it may possible to localize the activity that corresponds to the modulation of the loudness.

The results of these studies show a trend, although differences between individual studies, that tinnitus corresponds to an increased level of activity in number of auditory areas in the brain. They also found differences in activity in non-auditory areas (such as the frontal lobe, the limbic system and the cerebellum) that seem associated with tinnitus. None-auditory areas seem associated with tinnitus although the role of these non-auditory brain is not yet clear.

Nevertheless, it remains unclear whether the differences in neural activity between the subject groups are related to tinnitus or that they may have been caused by differences in the hearing levels or age between the groups. Hyperacusis, a reduced tolerance to loud sounds—often coinciding with tinnitus—may also responsible for the aberrant levels of activity.

## Increased sound-evoked responses

The first study (as described in chapter 3) studies a specific group of subject with lateralized tinnitus. Based on this lateralization of tinnitus, a corresponding lateralization at cortical levels was expected. This functional lateralization, on the contrary, was not apparent. The results, however, did show an increased sound-evoked response in the inferior colliculus (IC) of subjects with lateralized tinnitus as compared to those in a control group. Chapter 3

The results also showed that contra-lateral stimuli gave larger responses than ipsilateral stimuli. Moreover, 70 dB (SPL) stimuli gave larger responses than those of 40 dB (SPL).

In the IC of subjects with tinnitus, the pattern of responses was different; patients with tinnitus do not show the contra-lateral dominance of the responses. In addition to the

increase sound-evoked responses, we measured a difference in the response lateralization. A striking conclusion is that the lateralization of the response did not correspond to the lateralization of the tinnitus

## Lateralization and connectivity

Chapter 4 The response lateralization to sound may give a measure of the efficiency of the input from the periphery to the central nervous system. From the auditory peripheral system to the central auditory system there are generally speaking two pathways; contra-lateral excitatory pathways and ipsilateral inhibitory pathways. A reduction in the efficiency of this inhibitory pathway may (by a reduction of inhibition) theoretically lead to increased activity in ipsilateral auditory nuclei. This in turn leads to a reduction in the so-called lateralization index.

The lateralization index was determined for each nucleus in the auditory pathway. This index was systematically lower in the patient-group, but only significant at two levels: the right primary auditory cortex (PAC) and the right IC. This suggest that there is a reduced efficiency of the ipsilateral inhibitory afferent input to the IC. In contrast to the findings in chapter 3, there were no increase sound-evoked responses in the IC of patients.

In addition to this analysis, we studied the connectivity patterns between nuclei of the auditory pathway. The degree of influence of one nucleus onto another can be described in terms of correlation of the time-courses of these nuclei. This *functional connectivity* suggested that if nuclei are active at the same time, they may be functionally connected. Yet, correlation does not imply causality and cannot distinguish the direction of the stream of information between nuclei.

The partial correlation was used as a measure of *effective connectivity* to assess the influence that one nucleus has on another nucleus. The partial correlation is the correlation that remains between two nuclei after subtracting the influence of the other nuclei.

The functional connectivity in the auditory pathway was larger than the effective connectivity and suggests that a great deal of the correlation can be explained by the experimental paradigm that was used; presenting sound stimuli. The results showed a disturbed pattern of effective connectivity between the IC and the contralateral *medial geniculate body* (MGB) as well as between the left *cochlear nucleus* (CN) and the left primary auditory cortex. In particular, the disturbed effective connection between the IC and MGB is in agreement with previous findings; a reduced lateralization in subjects with tinnitus.

## Disturbed balance between somatosensory and auditory input

Chapter 5 Somatic tinnitus is a phenomenon which refers to tinnitus that is elicited or modulated by somatosensory modulation like e.g. jaw protrusion. The results demonstrate that over-

lap of somatosensory and auditory input can be measured in the auditory pathway; jaw protrusion caused a response in the auditory system and may explain the influence of jaw protrusion on the perceived loudness of tinnitus.

Overlap between the auditory modality and the somatosensory modality were found in the primary auditory cortex and the auditory association cortex. Interestingly, the only differences between subjects with tinnitus and controls were found in the CN and the IC. Jaw protrusion evoked in both ROIs a larger response in subjects with tinnitus compared to those in controls.

Our findings stress the importance of somatosensory interaction in the (extralemniscal or non-classical) auditory system in defining possible mechanisms underlying tinnitus. One hypothesis, relating tinnitus to changes in normal somatosensory integration, is that a change in input from the auditory system (due to e.g. noise-induced hearing loss) might influence the somatosensory input to the central nervous system. This thus form a neurophysiological basis for modulating perceptual characteristics of tinnitus. Especially our finding that jaw protrusion shows enhanced responses in the inferior colliculi and cochlear nuclei of subjects with tinnitus compared to controls underlines this hypothesis.

## The auditory pathway

Where the results of our fMRI findings were summarized in chapter 3–5 summarizes Chapter 6 chapter 6 the results from a study that used *Diffusion tensor imaging* (DTI) to gain insight in the anatomical pathway formed by white matter fiber bundles. DTI is a technique sensitive to the diffusion of water in tissue and can be used to track the anatomical pathway between two predefined areas. The first results shows that this method can be used to track part of the auditory pathway. The paths that the auditory cortex connect to the IC all pass the MGB of the thalamus. The structural properties of these paths were determined and compared between subject groups.

By quantifying the tracks that pair-wise connect the IC, AC and amygdala (AM), we were able to make comparisons between control subjects and tinnitus patients. These three ROIs were selected because they may play an important role in the mechanisms that lead to tinnitus. We found differences and similarities between tinnitus patients and healthy controls.

Significant differences in path strength between tinnitus patients and healthy controls were found for the left IC-AM connection, the right AC-IC connection, and the AC-AM connection for both hemispheres.

The difference in strength of the connection between auditory cortex and amygdala in subjects with tinnitus compared to controls indicates that the limbic system may indeed play a major role in tinnitus, especially concerning the emotional content of the percept of

tinnitus. Although cognitive therapies, focused on treating tinnitus by habituation, have been used for many years, no imaging study prior to the present one has shown a potential anatomical pathway that might function differently between tinnitus patients and normal hearing controls.

### **Between the ears?**

The experiments as described in this thesis show that there are subtle functional and structural differences between subjects with and without tinnitus. Tinnitus seems thus a pathology between the ears. Note that, the difference may occur as a response of the central nervous system to a peripheral hearing loss. This may cause a disruption—like with the amputation of a limb—of the normal input to the brains. Tinnitus seems to be consequence of the changes in the central nervous system that follow peripheral hearing loss.